REMARKS

Claims 1-4 are pending in the instant application. Claims 1-4 have been rejected. Claims 1, 2, and 4 have been amended. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Withdrawn Rejections

Applicant acknowledges the withdrawal of the rejection of claims 1-4 under 35 U.S.C. 112, second paragraph, as being indefinite.

II. Rejection of Claims Under 35 U.S.C. §112

Claims 1-4 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not disclosed in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner suggests that there is no support in the specification for a method for identifying compounds including cells containing interacting proteins comprising a Smad protein, a DNA-binding Smad co-repressor protein and a CtBP protein and the detection steps. In particular, it is suggested that the steps listed in the claims are not of record in the specification. Further, it is suggested that the amendments including the reporter and Smad-box containing promoter are not supported by the specification. Moreover, the Examiner suggests that the written description only sets forth wild-type dCtBP and does not disclose the plethora of genes that may be induced by TGF-β, activin or BMP. It is suggested that with the exception of

wild-type dCtBP, the skilled artisan cannot envision the detailed structure or function of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred. Applicant respectfully disagrees.

MPEP 2163 indicates that the basis of the written description requirement is that an Applicant's specification must convey with reasonable clarity *to those skilled in the art* that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991).

Applicant has identified the unique interaction between Smad proteins, DNA-binding Smad co-repressor proteins and CtBP proteins and the ability of these interacting proteins to mediate repression of genes that are negatively regulated by TGF-β signaling pathways. The specification as a whole, and in particular at pages 14 and 15, clearly teaches that, having appreciated this interaction between Smad proteins and co-repressor proteins such as DNA-binding Smad co-repressor proteins and CtBP proteins, inhibitors can be identified which "interact with Smad proteins to prevent interaction of CtBP with Smads or with DNA-binding co-repressors (*e.g.*, Evi-1, TGIF, SIP1 or Schnurri), or of formation of a DNA-bound complex containing Smads, CtBP and DNA-binding co-repressors" [emphasis added] and prevent repression of genes that are negatively regulated by TGF-β signaling pathways. Thus, one embodiment for identifying compounds that directly interact with a Smad protein or a DNA-binding Smad co-repressor protein encompasses the use of cells expressing these Smad, CtBP, and DNA-binding Smad co-repressor

proteins and a means for determining whether their interaction has been disrupted. Accordingly, in an effort to clarify that the cells containing interacting proteins comprising a Smad protein, a DNA-binding Smad co-repressor protein and a CtBP protein are expressing these proteins, Applicant has amended claims 1 and 2 to recite "expressing" rather than "containing".

Another embodiment of the assay of the instant invention is the use of a cell-based reporter construct employing luciferase or β-galactosidase reporter proteins to detect changes in TGF-β-dependent reporter expression in response to specific compounds (see paragraph bridging pages 14 and 15). In an earnest effort to more closely impart the type of promoter disclosed in the specification for use in accordance with the claimed method, Applicant has amended claim 1 to indicate that the reporter protein has a TGF-β-dependent promoter. Further, it would be clear to the skilled artisan that in order to "detect changes in TGF-β-dependent reporter expression in response to specific compounds", the level of transcription of the reporter in the cells must be measured before and after addition of the test compound. Assays using TGF-β-dependent reporter constructs to detect changes upon exposure to specific compounds are well-known to the skilled artisan. To illustrate, Su et al. ((2000) *Cancer Res.* 60:3137-3142; enclosed herewith) teach the use of a reporter construct containing Smad-binding elements (p6SBE-luc) responsive to TGF-β in the presence and absence of inhibitors to measure processes that result in the nuclear localization of Smad4 (see, *e.g.*, Figure 6). Using this screen, a novel histone deacetylase inhibitor, termed scriptaid, was identified which did not interfere with a further induction provided by stimulation of the

cognate signal transduction pathway (*i.e.*, TGF-β/Smad4). Accordingly, in view of the teachings of Su et al., the teachings of the instant specification, and the fact that the claimed subject matter need not be described literally in order for the disclosure to satisfy the description requirement (MPEP 2106), Applicant finds no basis for the Examiner's suggestion that persons skilled in the art would not recognize in Applicant's disclosure a description of the invention defined by the claims. Applicant believes that the essential features of the method of the invention (*i.e.*, cells expressing Smad, CtBP, and DNA-binding Smad co-repressor proteins and a TGF-β-dependent reporter construct) are supported by the basic teachings of the disclosure and what is well-established in the art of inhibitor screening with TGF-β-dependent reporter constructs.

Page 8, lines 22-25, teach that dCtBP in Drosophila and its mammalian homologues have been shown to have similar functions as co-repressors with the ability to bind histone deacetylase. Accordingly, to clarify the scope of the instant method, Applicant has amended claim 4 to indicate that the CtBP protein is dCtBP, CtBP2 or a functional mammalian homologue of dCtBP. As indicated in Applicant's response filed September 8, 2003, dCtBP, CtBP2 and functional mammalian homologues of dCtBP (*e.g.*, human CtBP, Accession No. U37408; rat CtBP, Accession No. NP_062074; and mouse CtBP, Accession No. AB033122) were well-known to the skilled artisan at the time of filing as general co-repressor proteins. Further, as disclosed at pages 2-3 of the instant disclosure, negative regulation of target genes (*e.g.*, c-myc, cyclin A, proteases that degrade components of the extracellular matrix such as collagen, and wingless) by TGF-β, BMP, and activin

signaling pathways was well-established at the time of filing. Applicant's invention is based on the novel finding that known regulatory proteins (*i.e.*, Smad proteins, DNA-binding Smad co-repressor proteins, and CtBP proteins) physically interact to mediate transcriptional repression in response to TGF-β, BMP, and activin signaling. Accordingly, while the essential features of the claimed method were individually known, they had not been previously documented to have the association set forth in the instant claims. Therefore, in light of the teachings of the instant specification and what was well-established in the art at the time of filing, Applicant has conveyed with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicant was in possession of the invention. Further, an Applicant need not have actually reduced the invention to practice prior to filing. The Courts have clearly held that "The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it". 822 F.2d at 1078, 3 USPQ2d at 1304 (quoting *In re Chilowsky*, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956)). See MPEP 2164.02.

In light of the present amendments and accompanying remarks, is respectfully requested that the rejections under 35 U.S.C. 112, first paragraph, be reconsidered and withdrawn.

III. Conclusion

The Applicants believe that the foregoing comprises a full and complete response to the Office Action of record.

Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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Date: **April 25, 2005**

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